REMARKS

Reconsideration and allowance are respectfully requested.

The Examiner's courtesy in granting the interview of October 18, 2001 is gratefully acknowledged. During the interview, he stated that he would rejoin method claims restricted to antigens derived from a pathogen. Applicants have agreed to provide the references missing from the Examiner's application files so the Information Disclosure Statement submitted on June 7, 2001 could be considered.

Claims 1-35 and 41-69 are pending. Applicants have canceled the non-elected claims without prejudice to future prosecution of that subject matter.

The amendments are supported by the original disclosure and, thus, no new matter has been added. If the Examiner should disagree, however, he is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response.

The specification has been amended to add a sequence identifier. Moreover, the claims have been amended to conform to the Examiner's restriction requirement as he stated it during the interview (i.e., rejoinder of method claims which are restricted to antigens derived from a pathogen). ADP-ribosylating exotoxins and derivatives thereof having adjuvant activity are described on page 16, line 3, to page 18, line 25, of the specification. If lipid vesicles (e.g., liposomes) are present in the formulation, at least some of the formulation's antigen is not encapsulated; unencapsulated antigen would be in solution and/or associated with the lipid vesicles (see page 20, lines 23-26, of the specification). Presentation of at least one antigen or epitope thereof is supported by page 6, lines 26-31, of the specification.

For claim 15, providing antigen in the form of live or attenuated live virus or virosome is described on page 6, lines 10-11, and page 14, line 15, of the specification.

Amended claim 27 and new claim 58 includes a cream, and new claim 57 is limited to a solution, in accordance with page 8, lines 19-20, of the specification. New claim 59 is supported by original claims 41-49.

ADP-ribosylating exotoxins and derivatives thereof (amended claims 22-26 and new claims 41-44 and 60-68) are described on page 16, line 3, to page 18, line 25, of the specification. New claim 45 is supported by page 6, lines 1-2, of the specification.

New claims 46-47 are complementary for the concept that a single molecule may contain both antigen and adjuvant properties, or not (see page 15, lines 13-15, of the specification). New claims 48-51 recite the molecular weight limitations described on page 6, lines 2-5, of the specification. Antigens may be expressed by a whole organism (new claim 52) in accordance with page 8, lines 5-6, of the specification.

New claims 53-56 and 69 are directed to using formulations without lipid vesicles in accordance with page 19, lines 10-18, of the specification. Claims 54-55 find support in original claims 5-6, respectively. Hydration (claims 56 and 69) is described on page 3, line 24, and page 8, lines 26-31, of the specification and the Examples.

Paper and computer readable forms of the Sequence Listing are being submitted herewith in response to the Examiner's requirement. The paper and computer readable forms of the Sequence Listing do not add new matter, and their contents are the same. It is respectfully submitted that this submission complies with 37 CFR § 1.821 et seq. Otherwise, prompt notice of any defects in the Sequence Listing is earnestly solicited and additional time is requested to comply.

35 U.S.C. 112 – Written Description

Claims 4 and 22-24 were rejected under Section 112, first paragraph, because the specification allegedly "does not contain a written description of the claimed invention." Applicants traverse.

Original claim 4 was incomplete as originally presented for examination. Unfortunately, the amendment to claim 4 made on June 7, 2001 was incorrect in asserting that a physical, chemical, electrical, or sonic penetration enhancer is being used with this version of transcutaneous immunization. As discussed with the Examiner during the interview, penetration enhancement and barrier disruption are the subject of Appln. No. 09/257,188. The present amendment of claim 4 corrects an obvious typographical error (i.e., the incomplete sentence) and finds support on page 22, lines 6-10, of the specification. The Examiner's alerting Applicants to this mistake is gratefully acknowledged.

Claims 22-24 include derivatives of ADP-ribosylating exotoxins having adjuvant activity. This finds support in the original disclosure on page 17, line 2, of the specification. Furthermore, Applicants' specification teaches particular derivatives as chemically-

or genetically-detoxified ADP-ribosylating exotoxins (page 17, lines 23-34, and page 18, lines 7-25) and chemical conjugates (page 18, lines 1-6). ADP-ribosylating exotoxin B subunits are other examples of derivatives with adjuvant activity (see page 16, lines 3-33, of the specification).

Withdrawal of the Section 112, first paragraph, rejection is requested.

35 U.S.C. 103 – Nonobviousness

Claims 1-12, 16-24 and 27-35 were rejected under Section 103(a) as allegedly being unpatentable over Domb or Paul et al. (primary references) in view of Marinaro et al. (secondary reference) and the alleged "admitted prior art on page 16 of the specification." Applicants traverse.

Claims 1-12, 16-24 and 27-35 were rejected under Section 103(a) as allegedly being unpatentable over Domb or Paul et al. (primary references) in view of Kosecka et al., the alleged "admitted prior art on page 16 of the specification," and Wille et al. (secondary references). Applicants traverse.

Applicants' independent claims are directed to methods of transcutaneous immunization in which "an effective amount of the antigen which is not encapsulated induces the immune response" (claim 1), "an effective amount of said one or more ADP-ribosylating exotoxins or derivatives thereof is not encapsulated" is applied (claim 30), "at least some antigen which is not encapsulated induces the immune response" (claims 31-32), and "an effective amount of at least one antigen derived from a pathogen and which is not encapsulated" is applied (claim 33). Moreover, independent claims 53 and 69 explicitly recite that lipid vesicles are not being used.

Domb compares lipospheres to other delivery systems (e.g., emulsions, vesicles, and liposomes) as carriers of antigen. Paul et al. compare transferosomes to the use of liposomes and mixed micelles as delivery systems. Both references rely on encapsulating antigen in a type of lipid vesicle (i.e., lipospheres for Domb and transferosomes for Paul et al.) to deliver antigen to the immune system. The Domb and Paul et al. lipid vesicles serve as carriers for encapsulated antigen.

In contrast, Applicants' claimed invention does not rely on lipid vesicles although they may be used in some embodiments (e.g., to hydrate the skin). Importantly, Appli-

cants' specification teaches that even if lipid vesicles are used for transcutaneous immunization, components of the formulation which are not encapsulated are effectively delivered to the immune system (page 20, lines 16-19 and lines 22-26). Example 2 of U.S. Patent 5,910,306 (incorporated by reference in Applicants' specification) demonstrated that washing away unencapsulated cholera toxin in liposome-containing formulations reduced the antigen-specific antibody response. Therefore, Applicants' invention is able to deliver antigen and/or adjuvant to the immune system without encapsulating them in lipid vesicles.

Antigen and/or adjuvant which is not encapsulated are the effective components for delivery to the immune system in claims 1 and 30-33. Domb and Paul et al. do not teach or suggest how antigen and/or adjuvant may be delivered without encapsulating the antigen in lipospheres or transferosomes, respectively. Furthermore, nothing of record teaches or suggests how to deliver antigen and/or adjuvant without their encapsulation in lipid vesicles.

Claims 53 and 69 explicitly recite that lipid vesicles are not used. Domb and Paul et al. do not teach or suggest how immunization may be accomplished without the use of lipospheres or transferosomes, respectively. Furthermore, nothing of record teaches or suggests how such lipid vesicles may be omitted without affecting delivery of antigen to the immune system.

The failure of Domb and Paul et al. to disclose all limitations of the invention as claimed is not remedied by the attempt in the Office Action to combine their disclosures with Marinaro et al., Kosecka et al., the "admitted prior art," and Wille et al. As noted above, the primary references use encapsulated formulations or lipid vesicles for drug delivery. But there is no teaching or suggestion in those references or the secondary references to deliver unencapsulated antigen or adjuvant to the immune system or to eliminate the use of lipid vesicles in the context of the claimed invention.

Finally, claims depending from Applicants' independent claims are also not made obvious by the cited references because the limitations of claims 1, 30-33, 53 and 69 are incorporated in the dependent claims.

Withdrawal of the Section 103 rejections is requested.

Double Patenting

Claims 1-4, 6-12, 16-21 and 27-35 were rejected under the judicially-created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-12 and 15-29 of Alving et al. (U.S. Patent 5,910,306) in view of Unger et al. (U.S. Patent 5,733,572) and in further view of Albert et al. (U.S. Patent 5,256,422). Applicants traverse because a terminal disclaimer is being submitted.

It should be noted that filing of a terminal disclaimer to overcome a rejection based on nonstatutory double patenting is not an admission that the rejection was proper. See *Quad Environmental Technologies Corp. v. Union Sanitary District*, 20 USPQ2d 1392, 1394-95 (Fed. Cir. 1991). The Court stated that the "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection." Thus, submission of a terminal disclaimer in accordance with M.P.E.P. § 804.02 is not an admission that the pending claims are obvious over the claims of the cited patents.

Withdrawal of the double patenting rejection is requested.

Conclusion

Having fully responded to all of the pending objection and rejections of the Office Action (Paper No. 18), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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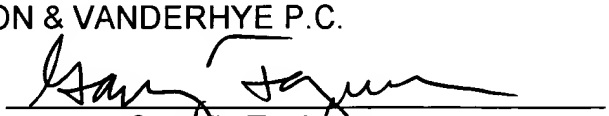
By: 

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APPENDIX

MARKED-UP VERSION TO SHOW CHANGES

IN THE SPECIFICATION

The specification is amended as follows.

Page 25, fourth paragraph starting on line 20:

Alving et al. (1986) injected liposomes comprising lipid A as an adjuvant for inducing an immune response to cholera toxin (CT) in rabbits and to a synthetic protein consisting of a malaria oligopeptide containing four tetra-peptides (Asn-Ala-Asn-Pro, SEQ ID NO:1) conjugated to BSA. The authors found that the immune response to cholera toxin or to the synthetic malaria protein was markedly enhanced by encapsulating the antigen within the liposomes containing lipid A, compared to similar liposomes lacking lipid A. Several antigens derived either from the circumsporozoite protein (CSP) or from merozoite surface proteins of *Plasmodium falciparum* have been encapsulated in liposomes containing lipid A. All of the malaria antigens that have been encapsulated in liposomes containing lipid A have been shown to induce humoral effectors (i.e., antigen-specific antibodies), and some have been shown to induce cell-mediated responses as well. Generation of an immune response and immunoprotection in an animal vaccinated with a malaria antigen may be assayed by immunofluorescence to whole, fixed malaria sporozoites or CTLs killing of target cells transfected with CSP.

IN THE CLAIMS

The claims are amended as follows.

1. (Amended Twice) A method of inducing an immune response comprising:

(a) applying a formulation to intact skin of an organism, wherein the formulation comprises (i) at least one [an] antigen which is derived from a pathogen and (ii) at least one [an] adjuvant comprising an ADP-ribosylating exotoxin or derivative thereof having adjuvant activity, and an effective amount of the antigen which is not encapsulated induces the immune response;

(b) activating a Langerhans cell with the at least one adjuvant [ADP-ribosylating exotoxin]; and

(c) presenting the at least one antigen or epitope thereof on a cell surface of the Langerhans cell to a lymphocyte, thereby inducing the immune response in the organism.

2. (Amended Twice) The method of claim 1, wherein the formulation consists essentially of antigen and adjuvant [ADP-ribosylating exotoxin].

4. (Amended Twice) The method of claim 1, wherein [further comprising use of] a physical, chemical, electrical, or sonic penetration enhancer is not used [to enhance said immune response by penetrating said organism's skin by the formulation].

11. (Amended) The method of claim 1, wherein the antigen is derived from a bacterium [source selected from the group consisting of a pathogen, a tumor cell, or a normal cell].

12. (Amended) The method of claim 1, wherein the antigen is derived from a [pathogen selected from the group consisting of bacterium,] virus[, fungus, and parasite].

13. (Amended) The method of claim 1, wherein the antigen is derived from a fungus or parasite [tumor antigen or an autoantigen].

15. (Amended) The method of claim 1, wherein the formulation comprises a live or an attenuated live virus or virosome; and the antigen is expressed by the live or attenuated live virus or virosome, which is not encapsulated.

22. (Amended Twice) The method of claim 1, wherein the ADP-ribosylating exotoxin is pertussis toxin or a [toxoid] derivative thereof having adjuvant activity.

23. (Amended Twice) The method of claim 1 [22], wherein the ADP-ribosylating exotoxin is cholera toxin (CT) [or cholera toxin B subunit (CTB)] or a [toxoid] derivative thereof having adjuvant activity.

24. (Amended Twice) The method of claim 1 [22], wherein the ADP-ribosylating exotoxin is *E. coli* heat-labile enterotoxin (LT) or a [toxoid] derivative thereof having adjuvant activity.

25. (Amended Twice) The method of claim 1 [22], wherein the ADP-ribosylating exotoxin is diphtheria toxin (DT) or a derivative thereof having adjuvant activity [in the formulation is provided as a nucleic acid encoding ADP-ribosylating exotoxin].

26. (Amended) The method of claim 1, wherein the ADP-ribosylating exotoxin is *Pseudomonas* exotoxin A or a derivative thereof having adjuvant activity [antigen in the formulation is provided as a nucleic acid encoding the antigen].

27. (Amended) The method of claim 1, wherein the formulation is a cream or gel or emulsion or ointment.

30. (Amended Twice) A method of immunization comprising applying a formulation to intact skin of an organism, wherein the formulation consists essentially of one or more ADP-ribosylating exotoxins or derivatives thereof having adjuvant activity, and an effective amount of said one or more ADP-ribosylating exotoxins or derivatives thereof is not encapsulated.

31. (Amended) A method of inducing an immune response comprising:

(a) applying a formulation to intact skin of an organism, wherein the formulation comprises (i) at least one [an] antigen which is derived from a pathogen and (ii) at least one [an] ADP-ribosylating exotoxin or derivative thereof having adjuvant activity, and at least some antigen which is not encapsulated induces the immune response; and

(b) inducing the immune response in the organism without perforating the skin, wherein the immune response is specific for the antigen.

32. (Amended Twice) A method of inducing an immune response comprising:

(a) applying a formulation to intact skin of an organism, wherein the formulation comprises (i) at least one [an] antigen which is derived from a pathogen and (ii) at least one [an] ADP-ribosylating exotoxin or derivative thereof having adjuvant activity, and at least some antigen which is not encapsulated induces the immune response;

(b) activating an antigen presenting cell with the at least one ADP-ribosylating exotoxin or derivative therof; and

(c) presenting the at least one antigen or epitope thereof on a cell surface of the antigen presenting cell to a lymphocyte, thereby inducing the immune response in the organism.

33. (Amended) A method of inducing an immune response comprising:

(a) applying epicutaneously on an organism an effective amount of at least one antigen derived from a pathogen and which is not encapsulated [epicutaneously on an organism],

(b) activating a Langerhans cell underlying the organism's skin with at least one [an] ADP-ribosylating exotoxin or derivative thereof having adjuvant activity,

(c) signaling the Langerhans cell to migrate to a lymph node of the organism and mature into a dendritic cell, and

(d) presenting the at least one antigen or epitope thereof on a cell surface of the dendritic cell to a lymphocyte; thereby inducing the immune response in the organism, wherein the immune response is specific for the at least one antigen.

Claims 36-40 are canceled without prejudice or disclaimer.

Claims 41-69 are added as new claims.

IN THE SEQUENCE LISTING

Paper and computer readable copies of the Sequence Listing are attached.